

TWENTY-DAY INTENSIVE ARSENOTHERAPY

THE SECONDARY REACTION IN TWENTY-DAY INTENSIVE ARSENOTHERAPY*

By ROBERT H. CREDE

Captain, United States Army Medical Corps

During the course of intensive arsenotherapy a syndrome which has been termed the "secondary reaction" or "secondary fever" develops in approximately 10-12 per cent of the number of patients under treatment. The term is purely one of convenience and this group of symptoms and signs has been given various names, such as "toxic erythema of the ninth day", "conjunctival injection" and "facial oedema syndrome".

With the twenty-day schedule of intensive arsenotherapy, the onset of the secondary reaction varies from the 5th to the 15th day of treatment. However, the majority of such reactions occur between the 8th and 12th days. It is of interest that similar reactions in shorter or in more prolonged schedules of treatment tend to appear during the same time interval; this fact suggests the possibility that the reaction may be a sequel of a sensitization which occurs during the first few injections. If a patient has received mapharsen previously, especially if given in a manner which might sensitize him, the secondary reaction may occur after the first or second injection.

As far as we can determine, there is no method by which this reaction can be predicted. The presence of fever is the one virtually constant sign. The febrile rise usually occurs from 2 to 4 hours after the daily injection, the temperature rising suddenly to varying heights (101°-105° F.). Concomitantly there is noted marked conjunctival injection, malaise, anorexia and headache. Occasionally nausea, vomiting and abdominal pain are present. In severe reactions there is moderate peri-orbital and facial oedema.

Nature of the secondary reaction

About 25 per cent of the number of patients who exhibit the secondary reaction manifest some cutaneous lesion. The patient may notice a pruritus at the onset of fever but the rash usually does not appear until about 24 hours after the febrile rise. A generalized reddish maculopapular rash is the most common type; occasionally, however, a miliaria-like eruption is seen, which may develop into confluent vesicular lesions with ensuing exfoliation. The duration of the eruption is usually from 24 to 48 hours, although in the more severe reactions it may persist for 4 or 5 days. Rarely the skin lesions are seen in the absence of fever, but subsequent therapy is based on the assumption that the lesions represent a manifestation of the secondary reaction.

Headache of varying severity is almost always present but, in my experience, has not been commonly the chief complaint. Spinal fluid examinations made routinely before and after treatment showed no significant changes in those patients who had secondary reactions.

Severe abdominal pain accompanied by vomiting was seen in 5 out of 47 cases of secondary reaction observed by me. In only one of these patients did clinical evidence of liver damage develop. Liver function tests made before and after treatment in 37 of these patients showed significant decrease in function in three of them, but only one patient showed an increased icteric index.

The conjunctival injection is accompanied by burning, lacrimation and photophobia. The conjunctival condition may persist after the patient becomes afebrile and will recur during the so-called "desensitization period". The patient will obtain symptomatic relief from 1 per cent ephedrine eye drops.

*Based on an address given to the Medical Society for the Study of Venereal Diseases, 29th January 1944.

Cause of the reaction

It is considered that the secondary reaction is the result of some sensitivity to or, less probably, actual poisoning by mapharsen. We know that inorganic arsenic is one of the most potent capillary poisons and that other manifestations of the secondary reaction, such as coryza, pharyngitis and localized oedema, are manifestations of arsenic poisoning. However, the clinical course, constant time of onset and similar reactions in different treatment schedules tend to support the hypothesis of a sensitivity reaction. The basis of the reaction seems to be a generalized dilatation of the vascular bed and it is probable that the changes which are visible in the conjunctivae are taking place throughout the body. The specific complication, for example, hepatitis, encephalopathy or agranulocytosis, probably depends upon which organ is the most susceptible to injury; it is therefore the so-called "shock site". Apparently the kidneys are not seriously damaged in this reaction, as the majority of patients have no proteinuria and haematuria has not been seen. No specific changes have been noted in the blood except agranulocytosis and a frequent rise in the number of non-filamented leucocytes without accompanying leucocytosis. This shift in the differential leucocyte count may be seen during, and occasionally prior to, a secondary reaction. It is considered that it may represent an early phase of agranulocytosis. There is so far no explanation of the transient adenopathy and pharyngitis which are seen in a few patients in the course of a secondary reaction.

Treatment of the secondary reaction

Treatment is non-specific: rest in bed, adequate fluid intake, a diet high in carbohydrate and sedation if needed. Ephedrine capsules orally or epinephrine (adrenaline) parenterally have been given with some subjective relief, but no significant alteration in the course of the reaction has been noted. Chemotherapy with the sulphonamides may be necessary in order to combat secondary infections, but chemotherapy for the secondary reaction *per se* is of no value. Sodium amytal (sodium salt of isoamylethylbarbituric acid) may be given intravenously if the patient has convulsive seizures due to an encephalopathy. Glutathione in its reduced form is a physiological antidote against arsenoxide, and it is known that amino-acid precursors of glutathione (glutaminic acid and cysteine) protect animals against the toxic effects of arsenoxide. In the future some such method as this may be tried in the treatment of the secondary reaction. The prime requisite, however, is good nursing care and I believe that our success in handling this reaction is due to the superior nursing care which our patients receive.

Type of fever and continuation of treatment

The continuation of treatment after the onset of secondary reaction depends entirely upon the judgment of the clinician. There are, however, a few principles which are of help in completing a greater number of treatments than is possible with the usual methods, and these are outlined below. The fever of the secondary reaction seems to be central in origin, as it does not respond to antipyretics and seems to decline concomitantly with the other signs of the secondary reaction. The fever may be divided roughly into two general types and the handling of the case depends upon which type is encountered.

(1) *Moderately severe reaction.* The first type is the fever that accompanies a moderately severe reaction; the temperature ranges from 101°-103° F. for 2-3 days and then drops to normal with a subsidence of all symptoms. In this type of reaction it is our practice to wait until the patient has been afebrile for 2-3 days and then to resume treatment with 0.006 gramme of mapharsen, that is approximately one-tenth of the usual dose. This amount of mapharsen is diluted in 10 cubic centimetres of distilled water and given in the same manner as the usual daily injection. The amount of mapharsen which is given is doubled daily (0.006, 0.012, 0.024, 0.048 gramme and so on) until the patient tolerates a full dose without ill effect. During the period of small dosage the patient may have a recurrence of the conjunctival injection, fever and other signs of the secondary reaction immediately after the

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injection. They are not severe, however, and the patient usually feels well on the following morning.

(2) *Severe reaction.* The second type is the fever that accompanies a severe secondary reaction, which may range from 103°-105° F. for 3-5 days. In this type of reaction one sees the serious complications : toxicodermal reactions, hepatitis, encephalopathy and agranulocytosis. These patients present a more difficult problem. It is our practice to wait from 4-6 days after the patient has become afebrile and symptom-free and then, if there has been no serious complication, to resume treatment with a 0.0006-gramme dose of mapharsen. This is approximately one-hundredth of the usual dose and is given in 10 cubic centimetres of distilled water, as described above. The amount of mapharsen is doubled daily until the patient tolerates the full dose without ill effect. During the period of small dosage the patient may suffer an exacerbation of his earlier symptoms but, as in the previous regime, he usually feels well the following morning. If, however, the reaction has been severe, the same dose may be given for a second time before the amount is doubled.

Conclusions

As the result of our experience we have been able to formulate a few simple therapeutic principles in regard to the secondary reaction and the subsequent treatment of the patient.

(1) If a patient has had a severe secondary reaction and treatment is resumed with a 0.006-gramme dose of mapharsen, the ensuing reaction may be as severe as was the original and may discourage the clinician from further treatment. When in doubt it is wise to resume treatment with a 0.0006-gramme dose of mapharsen.

(2) If treatment has been interrupted for some reason other than a secondary reaction, it is unwise to resume treatment with a full dose, as the patient is apt to have a reaction of the secondary type. It is our practice to resume treatment with a 0.006-gramme dose and the amount is increased daily as in the case of a moderately severe secondary reaction.

(3) After close observation we have been unable to discover any ill effects as the result of continuing treatment in patients who have had a severe secondary reaction.

(4) As far as we can determine, the only contraindications for further intensive arsenotherapy after the occurrence of a secondary reaction are the following : (a) hepatitis, (b) proved encephalopathy with persistence of symptoms and abnormal spinal fluid findings and (c) severe blood dyscrasias. For a patient of this type treatment may be continued with penicillin instead of the arsenicals.

By the use of the methods described above it has been possible to complete the twenty-day intensive course of treatment of 424 out of 428 patients.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES

PROGRAMME OF MEETINGS, 1945

All meetings are held at 11 Chandos Street, Cavendish Square, London, W.1, on Saturdays, at 2.30 p.m.

- March 24th Subject : *Early syphilitic infection treated with intensive arsenotherapy and penicillin.*
Speakers : Surg. capt. T. R. Lloyd-Jones and Surg. cmdr. F. G. Maitland.
- April 28th Subject : *Cutaneous manifestations in gonorrhoea.*
Speaker : Dr. A. H. Harkness.
- May 26th Subject : *The treatment of infective arthritis with special reference to hyperthermia.*
Speakers : Lt.-col. A. J. King, Maj. C. S. Nichol and Maj. D. I. Williams.
- July 28th ANNUAL GENERAL MEETING :
Subject : *Optimal methods of treatment of the venereal diseases with penicillin.*
Speakers : Col. D. M. Pillsbury and Maj. J. Marshall.